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Backward Bifurcation in a HIV/AIDS Epidemic Model with Age Structure I:

The Case of Proportionate Mixing

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1 Introduction

It has been widely recognized that in most epidemic model, the threshold theorem can be formulated by using the basic reproduction number R_0. The basic reproduction number is defined as the expected number of secondary cases produced, in a completely susceptible population, by a typical infected individual during its entire period of infectiousness. Then the epidemiological threshold criterion states that the disease can invade if $R_0 > 1$, whereas it cannot if $R_0 < 1$. In terms of dynamical system, the typical threshold theorem for epidemic models tells us that the disease-free steady state is globally asymptotically stable if $R_0 < 1$ and it is unstable if $R_0 > 1$. In many cases we can state more that there exists an endemic steady state with local stability if $R_0 > 1$ (Diekmann and Heesterbeek 2000). This means that the bifurcation of nontrivial steady state at $R_0 = 1$ is forward one when we take the basic reproduction number as a bifurcation parameter.

Though the above threshold criterion has been accepted as if it were a central dogma in epidemiology, it has been also pointed out by several authors that the backward bifurcation can occur for more complex epidemic models, hence endemic steady states could exist even in case that the basic reproduction number is less than one and the disease-free steady state is locally stable (Hadeler 1984, Hadeler and van den Driessche 1997, Huang, et al. 1992, Kribs-Zaleta and Velasco-Hernández 2000, Kribs-Zaleta and Martcheva 2002, Martcheva and Thieme 2002, van den Driessche and Watmough 2002).

The presence of a backward bifurcation has practically important consequences for the control of infectious diseases. If the bifurcation of endemic state

at $R_0 = 1$ is forward one, the size of infected population will be approximately proportional to the difference $|R_0 - 1|$. On the other hand, in a system with a backward bifurcation, the endemic steady state that exists for R_0 just above one could have a large infectious population, so the result of R_0 rising above one would be a drastic change in the number of infecteds. Conversely, reducing R_0 back below one would not eradicate the disease, as long as its reduction is not sufficient. That is, if the disease is already endemic, in order to eradicate the disease, we have to reduce the basic reproduction number so far that it enters the region where the disease-free steady state is globally asymptotically stable and there is no endemic steady state.

In this short note, we consider the bifurcation of endemic steady state in an age-structured model for HIV/AIDS epidemic in homosexual community. This model is an extension of the well known HIV/AIDS model with class age structure which has been already studied by several authors (Iannelli, et al. 1992, Thieme and Castillo-Chavez 1993). Though Huang, et al. (1992) have already shown that there could exist multiple endemic steady states for a multigroup SIR model, we can show that a backward bifurcation can occur even for a single community model with age structure.

2 The HIV/AIDS epidemic model with age structure

In the following, we consider an age-structured population of homosexual men with a constant birth rate. For simplicity, we assume that individuals have sexual contacts with each other at random and the duration of a partnership is negligibly short, so we neglect the effect of persistent partnership. We divide the sexually active homosexual population into two groups: S (uninfected but susceptible) and I (HIV infected). We do not introduce a latent class, since the latent period of AIDS is negligibly short in compare with its long incubation period. Thus all of I-individuals are infectious and will develop full-blown AIDS eventually. We assume that infected individuals with fully developed AIDS symptoms are sexually inactive and hence they are removed from the spread process.

Let $S(t,a)$ be the age-density of susceptible population at time t and age a and let B be the birth rate of susceptible population. Let a denote the age at infection for I-individuals and let $I(t,\tau;a)$ be the density of infected population at time t and *disease-age* (duration since infection) τ. Next let a be the age at which infected individuals have developed AIDS. Let $\mu(a)$ be the age-specific natural death rate (or the rate of terminating sexual life), $\gamma(a;\zeta)$ the rate of developing AIDS and let $\lambda(t,a)$ be the infection rate (the *force of infection*). Then the dynamics of the host population is governed by the following system:

$$S_t(t,a) + S_a(t,a) = -(\mu(a) + \lambda(t,a))S(t,a), \tag{2.1}$$

$$I_t(t,\tau;a) + I_\tau(t,\tau;a) = -(\mu(a+\tau) + \gamma(\tau;a))I(t,\tau;a), \tag{2.2}$$

$$S(t,0) = B, \tag{2.3}$$

$$I(t,0;a) = \lambda(t,a)S(t,a), \tag{2.4}$$

where $S_t = \partial S/\partial t$, etc. The force of infection $\lambda(t,a)$ is assumed to have the following expression:

$$\lambda(t,a) = \frac{C(P(t))}{P(t)} \int_0^\omega \int_0^b \beta(a,b,\tau) I(t,\tau;b-\tau) d\tau db, \tag{2.5}$$

where $P(t)$ is the total size of sexually active population $N(t,a) := S(t,a) + \int_0^a I(t,\tau;a-\tau)d\tau$ given by

$$P(t) := \int_0^\omega N(t,a)da = \int_0^\omega \left[S(t,a) + \int_0^a I(t,\tau;a-\tau)d\tau \right] da,$$

and $C(P)$ denotes the mean number of sexual partners an average individual has per unit time when the population size is P. Typical examples for $C(P)$ is given as follows:

$$(i)\ \ C(P) = \alpha_0 P, \quad (ii)\ \ C(P) = \frac{\alpha_0 \alpha_\infty P}{\alpha_0 P + \alpha_\infty}, \quad (iii)\ \ C(P) = \alpha_\infty.$$

The saturating contact law (ii) approaches to *mass action type contact law* (i) when $P \to 0$ and become the homogeneous of degree one (scale independent) contact law (iii) if $P \to \infty$. If we adopt the mass action assumption (i) and we assume that β can be factorized as $\beta(a,b,\tau) = \beta_1(a)\beta_2(b,\tau)$, our model can be reduced to a model studied by Gripenberg (1983).

In order to simplify system (2.1)-(2.5), let us introduce new functions s, i, n by

$$\begin{cases} S(t,a) = s(t,a)B\ell(a), \\ I(t,\tau;a) = i(t,\tau;a)B\ell(a+\tau)\Gamma(\tau;a), \\ N(t,a) = n(t,a)B\ell(a), \end{cases} \tag{2.6}$$

where $\ell(a)$ and $\Gamma(\tau;a)$ are the *survival functions* defined by

$$\ell(a) := \exp(-\int_0^a \mu(\sigma)d\sigma), \quad \Gamma(\tau;a) := \exp(-\int_0^\tau \gamma(\sigma;a)d\sigma).$$

Then $\ell(a)$ is the probability that an individual survives to age a under the natural death rate and $1-\Gamma(\tau;a)$ gives the *incubation distribution* for individuals infected at age a. Now we obtain the new simplified system for (s,i) as follows:

$$s_t(t,a) + s_a(t,a) = -\lambda(t,a)s(t,a), \tag{2.7}$$

$$i_t(t,\tau;a) + i_\tau(t,\tau;a) = 0, \tag{2.8}$$

$$s(t,0) = 1, \tag{2.9}$$

$$i(t,0;a) = \lambda(t,a)s(t,a), \tag{2.10}$$

$$\lambda(t,a) = \frac{C(P(t))}{P(t)} \int_0^\omega db \int_0^b d\tau K(a,b,\tau) i(t,\tau;b-\tau), \tag{2.11}$$

where

$$K(a,b,\tau) := \beta(a,b,\tau) B\ell(b) \Gamma(\tau;b-\tau),$$

$$P(t) = \int_0^\omega B\ell(a) \left[u(t,a) + \int_0^a \Gamma(\tau;a-\tau) i(t,\tau;a-\tau) d\tau \right] da.$$

Mathematical well-posedness of the system (2.7)-(2.11) can be shown by using classical integral equation approach or semigroup approach, though we do not deal with the time evolution problem here.

System (2.7)-(2.11) has a *disease-free* steady state $(s^*, i^*) = (1, 0)$. We here assume that the host population is in the steady state before the invasion of HIV. In the early stage of the epidemic, the dynamics of infected population can be described by the linearized equation at the disease-free steady state $(1, 0)$ as follows:

$$i_t(t,\tau;a) + i_\tau(t,\tau;a) = 0, \tag{2.12}$$

$$i(t,0;a) = \frac{C(P_0)}{P_0} \int_0^\omega \int_0^b K(a,b,\tau) i(t,\tau;b-\tau) d\tau db, \tag{2.13}$$

$$i(0,\tau;a) = i_0(\tau;a), \tag{2.14}$$

where i_0 is the initial data and P_0 denotes the size of totally susceptible host population given by $P_0 := \int_0^\omega B\ell(a) da$. From (2.12) and (2.13), we obtain the following integral equation for the boundary value $B(t,a) := i(t,0;a)$:

$$B(t,a) = G(t,a) + \frac{C(P_0)}{P_0} \int_0^t \int_\tau^\omega K(a,b,\tau) B(t-\tau, b-\tau) db d\tau, \tag{2.15}$$

where G is given by

$$G(t,a) := \frac{C(P_0)}{P_0} \int_t^\omega \int_\tau^\omega K(a,b,\tau) i_0(\tau - t; b-\tau) db d\tau.$$

Let us consider $G(t,a)$ and $B(t,a)$ as L^1-valued functions of $t > 0$ and let $\Pi(\tau)$ be a linear positive operator from $L^1(0,\omega)$ into itself defined by

$$(\Pi(\tau)\psi)(a) := \frac{C(P_0)}{P_0} \int_\tau^\omega K(a,b,\tau) \psi(b-\tau) db.$$

Then we can rewrite (2.15) as an abstract renewal integral equation in L^1:

$$B(t) = G(t) + \int_0^t \Pi(\tau)B(t-\tau)d\tau, \quad t > 0,$$

where we adopt the convention such as $G(t) = 0$ for $t > \omega$ and $\Pi(\tau) = 0$ for $\tau > \omega$. Though we omit the proof, we can show that under appropriate assumptions, the basic reproduction number is given by the spectral radius of the linear operator Ψ defined by $\Psi := \int_0^\infty \Pi(\tau)d\tau$, which is called as the *next generation operator* (Diekmann, et al. 1990, Diekmann and Heesterbeek 2000, Inaba 2002).

3 Bifurcation of endemic steady states

Let (s^*, i^*) be the steady state for system (2.7)-(2.11) and let $\lambda^*(a)$ be the force of infection in the steady state. Then it follows that

$$s^*(a) = e^{-\int_0^a \lambda^*(\xi)d\xi}, \quad i^*(\tau; a) = \lambda^*(a)s^*(a).$$

It follows from (2.11) that λ^* must satisfy the nonlinear integral equation as follows:

$$\lambda^*(a) = \frac{C(P(\lambda^*))}{P(\lambda^*)} \int_0^\omega db \int_0^b d\tau K(a,b,\tau)\lambda^*(b-\tau)e^{-\int_0^{b-\tau} \lambda^*(\xi)d\xi}, \qquad (3.1)$$

where $P(\lambda^*)$ denotes the size of steady state population with force of infection λ^* given by

$$P(\lambda^*) := \int_0^\omega B\ell(a) \left[e^{-\int_0^a \lambda^*(\xi)d\xi} + \int_0^a \Gamma(a-\tau;\tau)\lambda^*(\tau)e^{-\int_0^\tau \lambda^*(\xi)d\xi} d\tau \right] da.$$

It is clear that $\lambda^* = 0$ is a trivial solution corresponding to a disease-free steady state. Let us define a nonlinear positive operator F on $L^1(0,\omega)$ as follows:

$$F(\lambda)(a) := \frac{C(P(\lambda))}{P(\lambda)} \int_0^\omega db \int_0^b d\tau K(a,b,\tau)\lambda(b-\tau)e^{-\int_0^{b-\tau} \lambda(\xi)d\xi}, \quad \lambda \in L^1.$$

In most cases, under appropriate conditions for the integral kernel K, we can assume that F is completely continuous operator and we can observe that F maps a cone L^1_+ into a bounded set. The Frésche derivative of F at $\lambda = 0$, denoted by $F'[0]$, is no other than the next-generation operator Ψ. Then its Frobenius eigenvalue gives the basic reproduction number R_0, and if $R_0 = r(F'[0]) > 1$, then $\Psi = F'[0]$ does not have positive eigenvector with eigenvalue one, since the Frobenius eigenvector is the unique positive eigenvector in the positive cone. Therefore by using Krasnoselskii's theorem (Krasnoselskii 1964, Theorem 4.11), we can conclude that F has at least one positive (non-zero)

fixed point, which means that there exists an endemic steady state if $R_0 > 1$. For this type of argument, the reader may refer to Inaba (1990).

In order to see the possibility of multiple endemic steady state for our model as simply as possible, let us use the *proportionate mixing assumption*. That is, we assume that the kernel K can be decomposed as $K(a,b,\tau) = k_1(a)k_2(b,\tau)$. In this case, the range of the operator F is one-dimensional, spanned by k_1. Therefore if we insert $\lambda(a) = ck_1(a)$, $c > 0$ to the equation $\lambda = F(\lambda)$, we arrive at the characteristic equation for unknown number $c > 0$ as follows:

$$1 = \frac{C(P(ck_1))}{P(ck_1)} \int_0^\omega db \int_0^b k_2(b,\tau)k_1(b-\tau)e^{-c\int_0^{b-\tau} k_1(\xi)d\xi} d\tau. \tag{3.2}$$

If this characteristic equation has a positive root $c > 0$, ck_1 becomes a positive fixed point of F which gives the force of infection of an endemic steady state. Moreover, in this case the next generation operator is also one-dimensional:

$$(\Psi\lambda)(a) = \frac{C(P(0))}{P(0)} k_1(a) \int_0^\omega db \int_0^b d\tau k_2(b,\tau)\lambda(b-\tau).$$

Hence $k_1(a)$ is a positive eigenfunction of Ψ and its eigenvalue is given by

$$R_0 = \frac{C(P(0))}{P(0)} \int_0^\omega db \int_0^b k_2(b,\tau)k_1(b-\tau)d\tau.$$

Let us define two functions $f(c)$, $g(c)$ as

$$f(c) := \int_0^\omega \int_0^b k_2(b,\tau)k_1(b-\tau)e^{-c\int_0^{b-\tau} k_1(\xi)d\xi} d\tau db, \quad g(c) := \frac{P(ck_1)}{C(P(ck_1))}.$$

Then the characteristic equation is given by

$$f(c)/g(c) = 1, \tag{3.3}$$

and the basic reproduction number R_0 equals to $f(0)/g(0)$. Observe that

$$P(ck_1) = \int_0^\omega B\ell(a) \left[e^{-c\int_0^a k_1(\xi)d\xi} + \int_0^a \Gamma(a-\tau;\tau)ck_1(\tau)e^{-c\int_0^\tau k_1(\xi)d\xi} d\tau \right] da$$

$$= \int_0^\omega B\ell(a)\Gamma(a;0)da + \int_0^\omega e^{-c\int_0^\tau k_1(\xi)d\xi} d\tau \int_\tau^\omega B\ell(a) \frac{\partial\Gamma(a-\tau;\tau)}{\partial\tau} da.$$

Then we obtain that

$$P(\infty) = \int_0^\omega B\ell(a)\Gamma(a;0)da, \quad g(\infty) = \frac{P(\infty)}{C(P(\infty))} > 0.$$

From the above observations, it follows that $f(\infty)/g(\infty) = 0$, hence if $R_0 = f(0)/g(0) > 1$, then there exists at least one positive root $c > 0$ for the characteristic equation. Now we can prove the existence of multiple endemic steady states by subcritical bifurcation as follows:

Proposition 3. 1 *Suppose that $g'(0) < f'(0)$. If $R_0 = 1$, then there exists at least one endemic steady state. If $R_0 < 1$ and $|R_0 - 1|$ is small enough, then there exist at least two endemic steady states. If $g'(0) > f'(0)$, the bifurcation at $R_0 = 1$ is supercritical.*

Proof. Let us consider the characteristic equation with a parameter μ:

$$F(c, \mu) := \mu f(c)/g(c) - 1,$$

where we assume that the transmission kernel is normalized such that $f(0)/g(0) = 1$, then $F(0, 1) = 0$ and μ is the basic reproduction number R_0. It follows from our assumption that

$$\frac{\partial F}{\partial c}(0, 1) = \frac{f'(0) - g'(0)}{g(0)} > 0.$$

Then it follows from the Implicit Function Theorem that $F(c, \mu) = 0$ can be solved as $c = c(\mu)$ at the neighborhood of $(c, \mu) = (0, 1)$, and

$$\left.\frac{dc}{d\mu}\right|_{\mu=1} = -\frac{F_\mu(0, 1)}{F_c(0, 1)} = -\frac{1}{F_c(0, 1)} < 0.$$

Since $c(1) = 0$, for small $\epsilon > 0$, we have $c(\mu) > 0$ such that $F(c(\mu), \mu) = 0$ for $\mu \in (1 - \epsilon, 1)$. Let us fix such a $\mu \in (1 - \epsilon, 1)$ and consider $F(c, \mu)$ as a function of c. Then we know that $F(0, \mu) = \mu - 1 < 0$, $F(c(\mu), \mu) = 0$ and $F(\infty, \mu) = -1$. Moreover,

$$\frac{\partial F}{\partial c} = \mu \frac{f'(c)g(c) - f(c)g'(c)}{g(c)^2},$$

is positive at $c = c(\mu)$ if ϵ is small enough, because $\partial F/\partial c > 0$ at $c = 0$. Therefore we conclude that the basic reproduction number $R_0 = \mu$ is less than one but very near to the unity, there exists at least two endemic steady states which are given as positive roots of $F(c, \mu) = 0$. It is also clear that if $R_0 = 1$, then there exists at least one endemic steady state. Finally if $g'(0) > f'(0)$, we have $dc/d\mu|_{\mu=1} > 0$. Then for small ϵ, there is no $c(\mu) > 0$ such that $F(c(\mu), \mu) = 0$, $\mu \in (1 - \epsilon, 1)$. Then the possible bifurcation is supercritical. □

Corollary 3. 2 *If the transmission rate β and the developing rate γ are constant, the bifurcation at $R_0 = 1$ is supercritical.*

From the above result, we know that the subcritical bifurcation could occur when the basic reproduction number is passing through $R_0 = 1$. On the other hand, if the basic reproduction number is small enough, there is no endemic steady state and the disease-free steady state becomes globally asymptotically stable. For example, let us assume that $M := \sup_{x \geq 0} C(x)/x < \infty$, and define $\alpha > 0$ such that $\alpha = M^{-1}C(P(0))/P(0)$. Then it is easy to show that if $R_0 <$

α, there is no endemic steady state and the disease-free steady state is globally asymptotically stable (Inaba 2002).

For simplicity, we have only considered the proportionate mixing case above, by using the bifurcation theory of operators, it is not difficult to formulate a necessary and sufficient condition of the subcritical bifurcation for the general transmission rate. The general case will be reported in a separate note.

References

[1] O. Diekmann, J. A. P. Heesterbeek, J. A. J. Metz, (1990), On the definition and the computation of the basic reproduction ratio R in models for infectious diseases in heterogeneous populations, *J. Math. Biol.* 28: 365-382.

[2] O. Diekmann and J.A.P. Heesterbeek (2000), *Mathematical Epidemiology of Infectious Diseases: Model Building, Analysis and Interpretation*, John Wiley and Sons, Chichester.

[3] G. Gripenberg (1983), On a nonlinear integral equation modelling an epidemic in an age-structured population, *J. Reine. Angew. Math.* 341: 54-67.

[4] K. P. Hadeler (1984), Hysteresis in a model for parasitic infection, In *Numerical Methods for Bifurcation Problem*, T. Küpper, H. D. Mittelmann and H. Weber (eds.), pp. 171-180, Birkhäuser Verlag, Basel.

[5] K. P. Hadeler and P. van den Driessche (1997), Backward bifurcation in epidemic control, *Math. Biosci.* 146: 15-35.

[6] W. Huang, K. L. Cooke and C. Castillo-Chavez (1992), Stability and bifurcation for a multiple-group model for the dynamics of HIV/AIDS transmission, *SIAM J. Appl. Math.* 52(3): 835-854.

[7] M. Iannelli, R. Loro, F. Milner, A. Pugliese and G. Rabbiolo (1992), An AIDS model with distributed incubation and variable infectiousness: Applications to IV drug users in Latium, Italy, *Eur. J. Epidemiol.* 8(4): 585-593.

[8] H. Inaba (1990), Threshold and stability results for an age-structured epidemic model, *J. Math. Biol.* 28: 411-434.

[9] 稲葉 寿 (2002), 数理人口学, 東京大学出版会, 東京 [H. Inaba, *Suuri Jinkougaku* (Mathematical Models for Demography and Epidemics), University of Tokyo Press, 2002, Tokyo (in Japanese)]

[10] H. Inaba (2003), Backward bifurcation in a HIV/AIDS epidemic model with age structure II: The case of general transmission rate, to appear in Kôkyûroku, RIMS, University of Kyoto.

[11] M. A. Krasnoselskii (1964), *Positive Solutions of Operator Equations*, Noordhoff, Groningen.

[12] C. M. Kribs-Zaleta and J. X. Velasco-Hernández (2000), A simple vaccination model with multiple endemic states, *Math. Biosci.* 164: 183-201.

[13] C. M. Kribs-Zaleta and M. Martcheva (2002), Vaccination strategies and backward bifurcation in an age-since-infection structured model, *Math. Biosci.* 177/178: 317-332.

[14] M. Martcheva and H. R. Thieme (2002), Progression age enhanced backward bifurcation in an epidemic model with super-infection, *J. Math. Biol.* (in press).

[15] H. R. Thieme and C. Castillo-Chavez (1993), How may infection-age-dependent infectivity affect the dynamics of HIV/AIDS ?, *SIAM J. Appl. Math.* 53(5): 1447-1479.

[16] P. van den Driessche and J. Watmough (2002), Reproduction numbers and sub-threshold endemic equilibria for compartmental models of disease transmission, *Math. Biosci.* 180: